AIDSinfo

Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children

Varicella-Zoster Virus (Last updated November 6, 2013; last reviewed November 6, 2013)

Panel's Recommendations
• HIV-infected children and adults who have no evidence of immunity to varicella should avoid exposure to people with varicella or zoster **(AIII)**. Household contacts of HIV-infected patients should receive varicella vaccine if they lack evidence of immunity to avoid the possibility of transmitting wild-type varicella-zoster virus (VZV) to their HIV-infected contacts **(AIII)**.
• HIV-infected children aged 1 through 8 years without evidence of varicella immunity and whose CD4 T lymphocyte (CD4) cell counts are ≥15% should be considered for 2 doses of varicella vaccine, the first dose administered as early as age 12 to 15 months (or as soon as possible after the first birthday) and the second dose 3 months later **(BII)**. Older children with comparable levels of immune function (i.e., CD4 cell counts ≥200 cells/mm^3) who lack varicella immunity may be considered for 2 doses of varicella vaccine administered 3 months apart **(BIII)**.
• Combination measles-mumps-rubella-varicella vaccine should not be administered to HIV-infected children **(AIII)**.
• HIV-infected children with low CD4 percentages (<15%) should not be vaccinated against varicella **(AIII)**. Vaccination of such children can be safely undertaken after reconstitution of their immune systems (CD4 percentage ≥15%) with combination antiretroviral therapy (cART) for at least 3 months **(AII)**. Herpes zoster (HZ) vaccine should not be given to HIV-infected children **(AIII)**.
• HIV-infected children and adolescents who: 1) lack evidence of immunity to varicella, and   2) have a non-transient exposure to a contact with varicella or herpes zoster   should receive VZV immunoglobulin prophylaxis as soon as possible (ideally within 96 hours but potentially beneficial up to 10 days) after the close contact **(AII)**. Many experts limit this recommendation to varicella- or zoster-exposed HIV-infected children who are considered to be severely immunocompromised (i.e., CDC Immunologic Category 3) especially if they have high HIV viral loads and would be classified in CDC Clinical Category C **(BIII)**. When passive immunization is impossible, some experts recommend prophylaxis with acyclovir beginning 7 to 10 days after exposure, while others consider it prudent to wait until the first appearance of rash to start acyclovir therapy in VZV-susceptible and VZV-exposed, HIV-infected children **(CIII)**.
• Acyclovir is the drug of choice for treating VZV infection in HIV-infected children **(AI)**. Intravenous (IV) acyclovir is recommended for treating varicella in HIV-infected children with severe immunosuppression (i.e., CDC Immunologic Category 3) and those who have high fever, abdominal pain, respiratory symptoms, or numerous or deep, necrotic, or hemorrhagic skin lesions **(AIII)**. Oral acyclovir should only be used to treat varicella in HIV-infected children who are in CDC Immunologic Category 1 or 2 and who have mild varicella disease **(BIII)**.
• Acyclovir is the oral treatment of choice for zoster in HIV-infected children, given for 7 to 10 days, although longer durations of therapy should be considered if lesions are slow to resolve **(AII*)**. Oral administration of acyclovir for HZ is considered safe for children with mild to moderate immune suppression **(AII)**. Initial IV administration is recommended for HIV-infected children with severe immunosuppression (i.e., CDC Immunologic Category 3), extensive multidermatomal HZ, disseminated infection, visceral involvement, or otherwise complicated HZ **(AII*)**. It can also be considered for trigeminal nerve or sacral dermatomal involvement. IV acyclovir should be continued until cutaneous lesions and visceral disease are clearly resolving **(AIII)**, after which oral administration can be considered to complete the course of therapy—10 to 14 days in this situation **(AIII)**.
• Recommended treatment for progressive outer retinal necrosis includes optimization of cART and IV anti-VZV therapy that includes combinations of systemic antivirals (acyclovir or ganciclovir plus foscarnet), frequently with twice-weekly intravitreal injections of ganciclovir and/or foscarnet **(AIII)**. Adjunctive retinal surgery is sometimes recommended, along with corticosteroids and/or low-dose aspirin **(BIII)**. Acute retinal necrosis can be treated with IV acyclovir for 10 to 14 days, followed by prolonged (i.e., 4–6 weeks) oral treatment **(AIII)**.
• Alternatives to oral acyclovir in older adolescents include valacyclovir and famciclovir **(AI*)**.
• The treatment of choice for acyclovir-resistant VZV is IV foscarnet for 7 days **(AII*)** or until no new lesions for at least 48 hours **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials <u>in children</u>† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials <u>in adults</u> with clinical outcomes and/or validated laboratory endpoints with accompanying data <u>in children</u>† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies <u>in children</u>† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies <u>in adults</u> with long-term clinical outcomes with accompanying data <u>in children</u>† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

† *Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents*

Epidemiology

Varicella-zoster virus (VZV) infections are endemic worldwide. Prior to the universal administration of varicella vaccine, approximately 4 million cases of varicella occurred annually in the United States. The annual incidence in children aged <10 years was 9%; by adulthood more than 95% of individuals had antibodies to VZV, indicating prior primary infection.[1] In tropical and subtropical areas, varicella may be acquired later in childhood or early adulthood, but seroprevalence is high by age 30. Because of universal vaccination in the United States, the incidence of varicella and its associated morbidity and mortality have decreased by 74% to more than 90%.[2,3] VZV is transmitted by an airborne route.[4] It is highly contagious; clinical infection develops in about 80% of susceptible individuals exposed in a household.[5] Second attacks of varicella are uncommon.

Vertical mother-to-child transmission (MTCT) of VZV can occur. However, because most pregnant women are immune, varicella complicating pregnancy is unusual. Congenital varicella syndrome (multiple anomalies) occurs in approximately 2% (95% CI: 0%–5%) of infants born to women who have varicella at 13 to 20 weeks of pregnancy,[6,7] but is not seen in infants born to women who develop herpes zoster (HZ) during pregnancy. MTCT of VZV has not been reported in HIV-infected pregnant women who develop varicella.

VZV also can be transmitted to fetuses in late gestation, resulting in neonatal varicella. In mothers who develop varicella in the interval of 5 days before to 2 days after delivery, the attack rate for infants is approximately 20% and mortality, before the availability of antiviral therapy, was approximately 30%.[8] In comparison, if maternal varicella precedes delivery long enough to allow transfer of VZV antibodies across the placenta, infants can still develop varicella in the first 5 days of life, but it is rarely severe.

VZV causes both varicella (primary infection; chickenpox) and HZ, which represents reactivation of VZV that resides in a latent state in dorsal root and cranial sensory ganglia following varicella.

Once established, VZV latency persists for life, but reactivation to cause HZ occurs in 25% to 30% of people who had varicella. HZ is less contagious than varicella, but virus from HZ lesions can spread by direct contact or by an airborne route from immunocompetent and immunocompromised individuals to cause varicella in people who never had this infection. HZ occurs because the VZV-specific cellular immunity that is acquired with varicella and is needed to maintain latency declines with age. This same immunity is typically lost with HIV infection, explaining why HZ is common in HIV-infected people.[9,10] HZ was a very common complication in HIV-infected children in the era before combination antiretroviral therapy (cART) (approximately 10 cases/100 patient-years prior to 1996); the incidence of HZ remains at 2 to 3 cases per 100 patient-years in the cART era, which is 10 to 25 times higher than in the general population.[11-13] Risk factors for development of HZ include low incident or nadir CD4 T lymphocyte (CD4) cell count/percentage; high HIV viral load; and acquisition of varicella when the CD4 percentage is <15%.[13-15]

As in adults, the frequency of HZ recurrences in children correlates inversely with the CD4 cell count.[13,16] The incidence of HZ increases with age; this trend extends into adulthood, particularly in individuals younger than age 50.

In addition to cART and immune reconstitution, another reason for the declining incidence of HZ in HIV-infected children in countries with varicella vaccination programs is that many received the licensed varicella vaccine. This is associated with a decrease in HZ in HIV-uninfected children.[17] HZ is also less common in vaccinated HIV-infected children compared with those who had wild-type infection.[18]

Clinical Manifestations

The incubation period for varicella ranges from 10 to 21 days (average: 14 days) in immunocompetent children. Varicella can be associated with a brief prodrome of malaise and fever, followed by skin lesions that are more numerous on the face and trunk than on the extremities. These evolve over 5 days through macular, papular, vesicular, and pustular stages, culminating in crusts. Combinations of these types of lesions

are present simultaneously. Complications of varicella include superinfection of skin with bacterial pathogens, primarily staphylococci and streptococci. Clinically important systemic involvement can include neurologic manifestations, such as encephalitis, cerebellar ataxia, and transverse myelitis; hepatitis; pneumonia; and multiorgan failure with intravascular coagulation.

Varicella causes more morbidity in HIV-infected patients than in the general population. Initial reports of varicella in HIV-infected children suggested severe disease manifestations and chronic atypical skin lesions,[19,20] but more recent studies support less complicated courses, particularly in children receiving cART or who have higher CD4 cell counts at the time of infection.[14,21] However, the disease may last longer than normal, and the rate of complications is higher than in otherwise healthy children with varicella.[15,22]

Uncommonly, severely immunocompromised HIV-infected children can have persistent chronic infection, with continued appearance of new VZV lesions for >1 month after primary or recurrent infection.[20,23] The lesions are characteristically varicelliform at onset but evolve into non-healing ulcers or necrotic, crusted, and hyperkeratotic verrucous lesions. Chronic VZV was reported in 14% of HIV-infected children with VZV in the pre-cART era, usually in children with low CD4 cell counts.[16]

The classical presentation of HZ is an often painful or pruritic, vesicular dermatomal rash. Typically pain precedes the rash by 2 to 3 days. Less typical rashes, similar to those described for chronic varicella, including rashes that extend beyond dermatomal boundaries or are bilaterally distributed or generalized, can occur during HZ in HIV-infected children. They often have multiple recurrent episodes of HZ.[13,16] Disseminated zoster with multiorgan involvement can occur, with or without the typical rash of HZ. Encephalitis long after HZ, or without rash, has been reported in HIV-infected children.[24] Ruling out herpes simplex virus infection, which can be confused with VZV skin manifestations, is important in evaluating HIV-infected children with possible HZ infection.

Retinitis is a complication of VZV infection in HIV-infected children and adolescents[25,26] that can be confused with cytomegalovirus retinitis.[27] Progressive outer retinal necrosis is a VZV-associated entity that typically occurs with CD4 cell counts <50 cells/mm^3 and is often associated with HZ. Acute retinal necrosis can occur in HIV-infected children at any CD4 cell count. A rapid decrease in visual acuity, or occurrence of red eye or eye pain, should result in an immediate consultation with an ophthalmologist for diagnosis and specific therapy.

Diagnosis

Typical presentations of varicella and HZ are readily diagnosed clinically. Laboratory methods are required for atypical presentations, prolonged course, and non-response to therapy. VZV DNA polymerase chain reaction (PCR) is the most sensitive and specific method for diagnosing a VZV infection. It can provide an etiologic diagnosis within 24 to 48 hours and some research laboratories can differentiate between wild-type and vaccine strain VZV. In addition to lesion specimens, PCR can be applied to blood, cerebrospinal fluid, and pharyngeal and conjunctival swabs. Direct immunofluorescence for VZV antigen can be performed on cells collected from skin, conjunctiva, or mucosal lesion scrapings. Optimal sensitivity requires obtaining cells from the base of a lesion after unroofing a fresh vesicle. This method requires only a 3-hour turnaround time, but is significantly less sensitive (<75%) than PCR.[28,29] VZV can be isolated in cell culture from vesicular fluid or ulcer swabs, but the virus is labile and specimens must be processed rapidly. Typical cytopathic effect is noted only after 5 to 7 days. Even the more rapid shell vial method, which combines centrifugation of samples onto tissue culture monolayers and staining with fluorescein-conjugated monoclonal antibodies to detect synthesis of early VZV proteins, requires at least 48 hours and is less sensitive than PCR.[29] Culture methods are most often positive when an ulcer or vesicle is sampled, especially during the early days after illness onset and before initiation of antiviral therapy, whereas PCR often remains positive late in the illness and when scabs are used as a sample. PCR is critical for evaluating atypical presentations of HZ. Serologic tests are of little value in diagnosing active VZV infection in either HIV-infected or HIV-uninfected children.

Prevention Recommendations

Preventing Exposure

HIV-infected children who are susceptible to VZV infection (with no verified history of varicella or HZ and lack of evidence of appropriate vaccination or varicella immunity by a sensitive, specific antibody assay) should avoid exposure to individuals with varicella or HZ **(AIII)**. Commercially available VZV antibody assays can have false-negative and false-positive results, however, limiting the ability to determine varicella immunity with certainty.[30] Household contacts who lack evidence of immunity should receive varicella vaccine to reduce the possibility of transmitting wild-type VZV to their HIV-infected contacts **(AIII)**.[31] For the same reason, elderly household contacts should receive the HZ vaccine according to Advisory Committee on Immunization Practices recommendations.

Preventing Disease

Active Immunization

HIV-infected children aged 1 to 8 years without evidence of varicella immunity and whose CD4 percentages are ≥15% should be considered for two doses of varicella vaccine, the first dose administered as early as age 12 to 15 months or as soon as possible after the first birthday and the second dose 3 months later **(BII)**. Limited data from a clinical trial in HIV-infected children with these characteristics indicate that the vaccine was well-tolerated and that >80% of subjects had detectable VZV-specific immune responses (either antibody or cell-mediated immune response or both) at 1 year after vaccination.[32,33] This has been validated by other investigators.[34-36] In the absence of specific safety and immunogenicity data, the combination measles-mumps-rubella-varicella vaccine should not be administered in place of the single-antigen varicella vaccine to HIV-infected children **(AIII)**.

Data are limited on use of varicella vaccine in older HIV-infected children and adolescents. However, the safety of varicella vaccine in HIV-infected individuals aged >8 years who have comparable levels of immune function (i.e., CD4 cell count ≥200 cells/mm^3) is likely to be similar to that in children aged <8 years; however, based on observations with HIV-uninfected individuals, immunogenicity may be lower in older HIV-infected children, adolescents, and adults. Weighing the risk of severe wild-type VZV disease against the potential benefit of vaccination, older children with CD4 percentages ≥15% and CD4 cell counts ≥200 cells/mm^3 who lack varicella immunity can be considered for vaccination on the same schedule **(BIII)**. The response to vaccination should be optimal in patients on cART for an extended period and in those with high CD4 cell counts and very low viral loads. This should be considered in scheduling this (and other) immunizations.

Although HIV-infected children who are not severely immunocompromised tolerate the vaccine well, they, like healthy children, infrequently develop mild rashes around 2 to 3 weeks after vaccination. They rarely require antiviral therapy, and skin lesions usually clear in 3 to 5 days without treatment. Vaccine-strain VZV is susceptible to acyclovir. Because there is still varicella in some communities, VZV rashes (especially when they are extensive) that develop shortly after vaccination require virologic investigation to distinguish vaccine-associated rashes from those caused by wild-type VZV. HZ from the vaccine (Oka strain) is described in some healthy children and some children with acute lymphocytic leukemia.

HIV-infected children with low CD4 percentages (<15%) may rarely develop systemic disease (i.e., pneumonia and neurologic manifestations) from vaccine-strain VZV and should not be vaccinated against varicella **(AIII)**.[37] Vaccination of such children can be safely undertaken after stable reconstitution of their immune systems (CD4 percentage ≥15%) with cART for 3 months **(AII)**.[35] Efficacy of the varicella vaccine in HIV-infected children is suggested by long-term follow-up studies of vaccinees at several institutions.[12,18] Vaccination was >80% effective against varicella and no cases of HZ were observed in vaccinees. This compares favorably with the efficacy in vaccinated healthy children (after one dose) and in children with underlying leukemia (after two doses), where an efficacy of 80% to 85% was observed for prevention of clinical infection. In vaccinated HIV-uninfected children, most breakthrough varicella cases are mild, with

few lesions (commonly <50), less fever, and a shorter duration of illness.[31,38]

Because HZ vaccine is licensed only for use in healthy people aged ≥50 years to prevent HZ and has not been studied in HIV-infected children, it should not be given to HIV-infected children **(AIII)**.

Passive Immunization

HIV-infected children and adolescents who

1) lack evidence of immunity to varicella (as defined above), and

2) have a non-transient exposure to a contact with varicella or herpes zoster

should receive human VZV immunoglobulin (VariZIG) prophylaxis as soon as possible after the close contact, ideally within 96 hours but potentially beneficial up to 10 days[39,40] **(AII)**. Many experts limit this recommendation to varicella- or zoster-exposed HIV-infected children who are considered to be severely immunocompromised (i.e., in the Centers for Disease Control and Prevention [CDC] Immunologic Category 3), especially if also classified as CDC Clinical Category C[41] and experiencing a high HIV RNA plasma viral load **(BIII)**. When passive immunization is not possible, some experts recommend oral acyclovir for post-exposure prophylaxis (see below) for less immunocompromised HIV-infected patients. Passive immunization is achieved with VariZIG, a lyophilized preparation which, when properly reconstituted, is a 5% solution of hyperimmune Immunoglobulin G that can be administered intramuscularly. Previously available under an investigational new drug application expanded access protocol, VariZIG was approved by the FDA in December 2012. It is now available commercially and can be obtained 24 hours a day from the sole authorized U.S. distributor (FFF Enterprises, Temecula, California) at 1-800-843-7477 or online at http://www.fffenterprises.com. The duration of the incubation period for varicella may be prolonged up to 28 days after VariZIG administration, thus also extending the period of potential infectiousness. Subsequent active immunization, provided the vaccine is not contraindicated, should be delayed for 5 months. An alternative to VariZIG is intravenous immune globulin (IVIG), 400 mg/kg body weight, administered once as soon as possible (ideally within 96 hours after exposure). Patients who have received this dose of IVIG within the prior 3 weeks should be protected.

Post-Exposure Antiviral Prophylaxis

Several small studies suggest that post-exposure prophylaxis with acyclovir in healthy children often prevents or attenuates varicella.[42-44] Note that this approach is dependent upon adequate specific immune responses developing in exposed children during the incubation period. Thus, when passive immunization is not possible, some experts recommend prophylaxis with oral acyclovir 20 mg/kg body weight (maximum dose 800 mg), administered 4 times daily for 7 days, beginning 7 to 10 days after exposure.[45] The use of acyclovir for prophylaxis in HIV-infected, VZV-exposed children has not been studied. For that reason, some experts consider it prudent to wait until rash appears to start acyclovir therapy in VZV-susceptible and VZV-exposed, HIV-infected children who were not given passive immunization **(CIII)**.

Post-Exposure Prophylaxis with Varicella Vaccine

Post-exposure prophylaxis with varicella vaccine has been successfully used in HIV-uninfected children and adults.[46] However, this preventive approach is predicated on a prompt and robust immune response, which is why it has not been studied in HIV-infected patients and is not recommended.

Treating Disease

On the basis of controlled trials in children with malignancies, and response to therapy in HIV-infected children severely ill with varicella,[19] acyclovir is the drug of choice for treating VZV infections **(AI)**. Acyclovir should be initiated as soon as possible after varicella lesions appear. In immune competent children, new lesions can continue to appear for 72 hours after initiation of acyclovir and crusting of all

lesions may take 5 to 7 days. Intravenous (IV) acyclovir is recommended for treating varicella in HIV-infected children with severe immunosuppression (i.e., CDC Immunologic Category 3) and those who have high fever, abdominal pain, respiratory symptoms, or numerous or deep, necrotic, or hemorrhagic skin lesions **(AIII)**. For children aged <1 year, the dose of acyclovir is 10 mg/kg body weight administered IV every 8 hours as a 1-hour infusion. Some health-care providers administer the same dose to older children, while others base the dose of acyclovir in older children on body surface area (500 mg/m^2 IV every 8 hours as a 1-hour infusion).[45] Administration is for 7 to 10 days, provided that new lesions have ceased to appear for at least 48 hours. Oral administration should only be used to treat varicella in HIV-infected children who are in CDC Immunologic Category 1 or 2 and who have mild varicella disease **(BIII)**.

Acyclovir 20 mg/kg body weight (800 mg maximum dose) administered 4 times per day for 7 to 10 days is the oral treatment of choice for HZ in HIV-infected children, although longer therapy should be considered when lesions are slow to resolve **(AII*)**. Oral administration of acyclovir for HZ is considered safe because the risk of disseminated, life-threatening disease is lower with HZ than with varicella. However, initial IV administration is recommended for HIV-infected children with severe immunosuppression (i.e., CDC Immunologic Category 3), extensive multidermatomal HZ, disseminated infection, visceral involvement, or otherwise complicated HZ **(AII*)**. It also can be considered for trigeminal nerve or sacral dermatomal involvement. IV acyclovir should be continued until cutaneous lesions and visceral disease are clearly resolving **(AIII)**, after which oral administration can be considered to complete the course of therapy—10 to 14 days in this situation **(AIII)**. Doses of IV acyclovir for treating HZ are the same as those for treating varicella.

Progressive outer retinal necrosis is rapidly progressive and prognosis for visual preservation is poor despite aggressive therapy. Optimal therapy has not been defined.[25,47,48] Regardless of specific VZV antiviral therapy, optimization of cART is recommended. Most experts recommend IV anti-VZV therapy that includes combinations of systemic antivirals (acyclovir or ganciclovir plus foscarnet), frequently with twice-weekly intravitreal injections of ganciclovir and/or foscarnet **(AIII)**.[49] Adjunctive retinal surgery is sometimes recommended, along with corticosteroids and/or low-dose aspirin for associated occlusive vasculopathy and optic neuropathy **(BIII)**. In contrast, acute retinal necrosis appears more responsive to high-dose IV acyclovir (10–15 mg/kg body weight IV every 8 hours for 10–14 days), followed by prolonged (i.e., 4–6 weeks) oral treatment with acyclovir, or valacyclovir for older patients **(AIII)**.[49]

Alternatives to oral acyclovir in older adolescents and adults include valacyclovir and famciclovir **(AI*)**. Valacyclovir is a prodrug of acyclovir with improved bioavailability that is rapidly converted to acyclovir after absorption. Sufficient information exists to support the use of valacyclovir in children, especially given its two- to three-fold improved bioavailability compared with acyclovir, at a dose of 20 mg/kg body weight (maximum dose 1 g) three times a day.[50,51] However, because no pediatric formulation is available, valacyclovir can generally only be used for children old enough to swallow the large valacyclovir tablets. Alternatively, crushed valacyclovir tablets, which can be used to make an extemporaneous suspension, provide good bioavailability.[52] Data on the pharmacokinetics and dosing of famciclovir in children are insufficient to make recommendations, and no pediatric preparation is available.[53]

Monitoring and Adverse Events, Including IRIS

Acyclovir is excreted primarily by the kidney; as a result, dose adjustment based on creatinine clearance is needed in patients with renal insufficiency or renal failure. Primary toxicities of acyclovir are phlebitis (with IV administration), renal toxicity, neutropenia, nausea, vomiting, and rash. Toxicities are similar for valacyclovir. If possible, avoid other nephrotoxic drugs when acyclovir is administered. IV acyclovir must be adequately diluted and administered slowly over 1 to 2 hours. Adequate hydration should be assured and may require IV fluid administration for ill patients. For infants and children receiving high-dose IV acyclovir, monitoring of the complete blood count (CBC) and renal function is recommended at initiation of treatment and once or twice weekly for the duration of treatment, particularly for those with underlying renal dysfunction and those receiving prolonged therapy. Periodic monitoring of CBCs and renal function is also recommended for children receiving prolonged oral therapy.

HZ has been considered an immune reconstitution inflammatory syndrome event in numerous reports where the incidence of HZ was increased transiently after institution of cART.[54] However, an analysis comparing HZ incidence rates in the 3 months prior to cART with HZ incidence in the 3 months after cART indicated no difference.[13] This suggests that the high incidence occurring in the 3 months after cART represents persistence of the inability to develop a robust VZV-specific cell-mediated immune response in this early post-cART period. The incidence of HZ falls in the subsequent follow-up period as immune reconstitution proceeds. This relationship has been demonstrated with numerous opportunistic infections[55] and confirmed for HZ.[12]

Managing Treatment Failure

Children who continue to develop lesions, whose lesions fail to heal, or whose lesions progress after 7 days of treatment may be infected with acyclovir-resistant VZV.[56] This reflects the fact that acyclovir is a virostatic drug, and that such patients have inadequate VZV-specific cell-mediated immunity to rapidly clear the VZV infection. If possible, a lesion culture should be obtained and, if virus is isolated, susceptibility testing should be performed to confirm drug resistance. This may be difficult to arrange and will involve significant delay. Thus, the decision to change therapy is often based on clinical observations. All acyclovir-resistant VZV strains are resistant to valacyclovir, famciclovir, and ganciclovir. The therapeutic choice for acyclovir-resistant VZV is foscarnet 40 to 60 mg/kg body weight, which should be administered IV 3 times daily for 7 days **(AII*)** or until no new lesions have appeared for at least 48 hours **(AIII)**.[49,57] Foscarnet should be administered slowly IV over the course of 2 hours (no faster than 1 mg/kg/minute).

Foscarnet has significant nephrotoxic potential; ≥30% of patients experience increases in serum creatinine levels. It also causes serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) in many patients, and secondary seizures or cardiac dysrhythmias can occur. Abnormal liver transaminases and central nervous system symptoms can occur. Infusing foscarnet with saline fluid loading can minimize renal toxicity, and infusion through a central venous catheter can avoid thrombophlebitis. Doses should be modified in patients with renal insufficiency (see package insert). For patients receiving foscarnet, CBCs, serum electrolytes, and renal function should be monitored at least 2 to 3 times per week during induction therapy and once weekly thereafter.

Preventing Recurrence

No preventive measures are available for HZ in HIV-infected children and adolescents. However, varicella vaccination reduces the incidence (perhaps severity) of HZ compared with that in healthy or HIV-infected children who had natural infection.[12,17,18] The likelihood of initial or recurrent attacks of HZ is reduced with effective cART.[13] A vaccine to prevent HZ has been approved for use in immunocompetent adults aged ≥50 years. Data regarding safety and efficacy of this vaccine in HIV-infected persons of any age are lacking, and use of the vaccine in HIV-infected patients is not recommended. However, prospective clinical trials are under way to evaluate the safety and immunogenicity of the HZ vaccine in HIV-infected adults.

Discontinuing Secondary Prophylaxis

Not applicable.

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Indication	First Choice	Alternative	Comments/Special Issues
Pre-Exposure Prophylaxis	Varicella vaccine	N/A	See Figures 1 and 2 for detailed vaccine recommendations.
Primary (Post-Exposure) Prophylaxis	VariZIG 125 IU/10 kg body weight IM (maximum 625 IU), administered ideally within 96 hours (potentially beneficial up to 10 days) after exposure	• If VariZIG cannot be administered within 96 hours (up to 10 days), IVIG 400 mg/kg body weight, administered once should be considered. IVIG should ideally be administered within 96 hours of exposure • When passive immunization is not possible, some experts recommend prophylaxis with acyclovir 20 mg/kg body weight/dose (maximum dose 800 mg), administered QID for 7 days, beginning 7–10 days after exposure	Primary Post-Exposure Prophylaxis Indicated for: • Patients with substantial exposure to varicella or zoster with no verified history of varicella or zoster or who are seronegative for VZV on a sensitive, specific antibody assay or who lack evidence of vaccination. Many experts limit this recommendation to varicella or zoster-exposed HIV-infected children who are considered to be severely immunocompromised, (i.e., in CDC Immunologic Category 3), especially if also classified as CDC Clinical Category C[a] and experiencing a high HIV RNA plasma viral load **(BIII)**. • Some experts start acyclovir at first appearance of rash. **Note:** To obtain VariZIG, contact FFF Enterprises at 1-800-843-7477 or http://www.fffenterprises.com. [a] CDC. Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. Official authorized addenda: human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9-CM. *MMWR Morb Mortal Wkly Rep.* 1994;43:1-19. Available at http://www.cdc.gov/mmwr/PDF/rr/rr4312.pdf.
Secondary Prophylaxis	N/A	N/A	There is no indication for secondary prophylaxis

Indication	First Choice	Alternative	Comments/Special Issues
Treatment	Chickenpox *Children with No or Moderate Immune Suppression (CDC Immunologic Categories 1 and 2) and Mild Varicella Disease:* • Acyclovir 20 mg/kg body weight/dose by mouth (max 800 mg/dose) QID for 7–10 days and until no new lesions for 48 hours *Children with Severe Immune Suppression (CDC Immunologic Category 3):* • Acyclovir 10 mg/kg body weight 500 mg/m^2/dose IV every 8 hours for 7–10 days and until no new lesions for 48 hours Zoster *Children with Uncomplicated Zoster:* • Acyclovir 20 mg/kg body weight/dose (max 800 mg/dose) by mouth QID for 7–10 days. *Children with Severe Immunosuppression (CDC Immunologic Category 3), Trigeminal or Sacral Nerve Involvement, Extensive Multidermatomal, or Disseminated Zoster:* • Acyclovir 10 mg/kg body weight/dose IV every 8 hours until cutaneous lesions and visceral disease are clearly resolving, then can switch to acyclovir by mouth to complete a 10- to 14-day course *Children with Progressive Outer Retinal Necrosis:* • Ganciclovir 5 mg/kg body weight/dose IV every 12 hours, **plus** • foscarnet 90 mg/kg body weight/dose IV) every 12 hours, **plus** • ganciclovir 2 mg/0.05 mL intravitreal twice weekly and/or foscarnet 1.2 mg/0.05 mL intravitreal twice weekly *Children with ARN:* • Acyclovir 10–15 mg/kg body weight/dose IV every 8 hours daily for 10–14 days, **followed by** Oral valacyclovir 1 g/dose TID for 4–6 weeks (for children old enough to receive adult dose). Alternative oral acyclovir dose: 20 mg/kg body weight/dose QID for 4–6 weeks	Patients Unresponsive to Acyclovir: • Foscarnet (40–60 mg/kg body weight/dose IV every 8 hours) for 7-10 days or until no new lesions have appeared for 48 hours	In children ≥1 year of age, some experts base IV acyclovir dosing on body surface area (500 mg/m^2 body surface area/dose IV every 8 hours) instead of body weight. Valacyclovir is approved for use in adults and adolescents with zoster at 1 g/dose by mouth TID for 7 days; the same dose has been used for varicella infections. Data on dosing in children are limited and there is no pediatric preparation, although 500 mg capsules can be extemporaneously compounded to make a suspension to administer 20 mg/kg body weight/dose (maximum dose 1 g) given TID (see prescribing information). Famciclovir is approved for use in adults and adolescents with zoster at 500 mg/dose by mouth TID for 7 days; the same dose has been used for varicella infections. There is no pediatric preparation and data on dosing in children are limited; can be used by adolescents able to receive adult dosing. Involvement of an ophthalmologist with experience in managing herpes zoster ophthalmicus and its complications in children is strongly recommended when ocular involvement is evident. Optimal management of PORN has not been defined.

Key to Acronyms: ARN = acute retinal necrosis; CDC = Centers for Diseases Control and Prevention; IM = intramuscular; IU = international units; IV = intravenous; IVIG = intravenous immunoglobulin; PORN = progressive outer retinal necrosis; QID = four times a day; TID = three times daily; VariZIG = varicella zoster immune globulin; VZV = varicella zoster virus